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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/753,752	01/02/2001	Jay M. Short	DIVER1200-3	1890

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LISA A. HAILE, PH.D.
GRAY CARY WARE & FREIDENRICH LLP
SUITE 1100
4365 Executive Drive
San Diego, CA 92121

EXAMINER	
RAMIREZ, DELIA M	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 07/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/753,752	SHORT, JAY M.	
	Examiner	Art Unit	
	Delia M. Ramirez	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 June 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

Claims 1-5 are pending.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action /has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/17/2004 has been entered.

It is noted that the claims and arguments submitted under 37 CFR 1.114 were previously presented on 9/22/2003 in response to the Final Office action mailed on 6/18/2004. The amendment filed by Applicants on 9/22/2003 was entered and addressed in the Advisory Action mailed on 10/16/2003.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Terminal Disclaimer

1. As indicated in the Advisory Action mailed on 10/16/2003, the terminal disclaimer filed on 9/22/2003 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of U.S. Patent No. 6280926, 6168919, 5958672, 6,528,249, 6,566,050, or any patent granted on Application Number 09/421629, 09/467740, 09/875412, has been reviewed and is accepted. The terminal disclaimer has been recorded.

Claim Rejections - 35 USC § 112, First Paragraph

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. As indicated in the Advisory Action mailed on 10/16/2003, claims 1-5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claims 1-5 as amended are now directed to a process of identifying/screening clones having DNA derived from two or more uncultivated organisms. The Examiner has not been able to locate adequate support for a process for identifying/screening clones having DNA derived from two or more uncultivated organisms. Thus, there is no indication that the claimed processes were within the scope of the invention as conceived by Applicants at the time the application was filed. Accordingly, Applicants are required to cancel the new matter in response to this Office Action.

4. As indicated in the Advisory Action mailed on 10/16/2003, claims 1-5 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection has been discussed at length in the Office Action mailed on 12/27/2002.

5. Applicants argue that given the knowledge of the art in regard to enzyme activity tests, one can easily determine whether every clone in the library was given the same positive signal or displaying the same enzymatic characteristic, or whether one or more particular cells were producing a positive response that was not common to the whole library. Applicants submit that a subtraction technique does not require use of a host cell whose complete genome is known but

can be accomplish by ignoring or subtracting out the enzymatic activities that are commonly produced by the host cells. According to Applicants one of skill in the art does not need to know the exact temperature or pH at which the host's enzymes cease to function to use the subtraction method since one can increase or lower pH or temperature until enzymatic activity common to all of the host cells has been eliminated and only the specific expression products that remain at extreme pH and temperature are attributable to the recovered DNA. Applicants also submit that false positives can also be detected in a similar procedure.

6. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection. It is noted that the claims as written encompass any host cell and any enzymatic activity. While the Examiner acknowledges that one of skill in the art can raise or lower pH or temperature and eliminate all enzymatic activity in a host cell, it is unclear as to how one can determine which are the temperatures or pH conditions which would eliminate only the host's endogenous enzymatic activity and not that which can be attributed to the "recovered DNA" without some knowledge or guidance as to which enzymes are endogenous to that host cell, such that a temperature/pH range could be established for endogenous enzymatic activity for a particular host cell. If, for example, the host cells and the organisms from which the "recovered DNA" is isolated have a similar temperature/pH range in regard to their endogenous enzymatic activity, it is unclear as to how one can use the subtraction method indicated by Applicants using temperature/pH. In addition, even if one could use the subtraction method as Applicants assert, the specification is silent in regard to how to detect enzymatic activity which is only found at pH and temperatures which are not extremes, nor does it teach how to detect false positive under those conditions. Since the claims encompass any enzymatic activity and any host cell, one cannot reasonably conclude that the claimed invention is adequately described.

7. As indicated in the Advisory Action mailed on 10/16/2003, claims 1-5 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for identifying E. coli clones of a recombinant DNA library derived from an uncultivated microorganism wherein the clones are screened for hydrolase activity after heating to 70 C, does not reasonably provide enablement for a method of identifying clones of a recombinant DNA library derived from an uncultivated microorganism wherein the clones are tested for expression of any enzyme having any enzymatic characteristic or any protein having any characteristic. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. This rejection has been discussed at length in the Office Action mailed on 12/27/2002.

8. Applicants argue that the claims as amended now refer to enzymatic activity/characteristic and not just any protein characteristic/activity. Furthermore, Applicants submit that the remarks made in regard to the written description rejection also apply to the enablement rejection. Applicants also submit that in regard to claims 4 and 5, detection of enzymatic activity under extreme conditions, such as low/high pH or temperature, is routine. Therefore, Applicants request withdrawal of the enablement rejection.

9. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the enablement rejection. While it is agreed that the claims are now limited to enzymatic activity/characteristics, and that detection of enzymatic activity at low/high temperature/pH is routine if the enzymatic assay is known, the Examiner disagrees with Applicant's contention that the claimed process is enabled. As indicated above, it is unclear as to how one can one can determine which are the temperatures or pH conditions which would eliminate only the host's endogenous enzymatic activity and not that which can be attributed to the "recovered DNA" without some knowledge or guidance as to which enzymes are endogenous to that host cell, such that a temperature/pH range could be established for endogenous enzymatic

activity for a particular host cell. See discussion above. The specification is silent in regard to how to detect enzymatic activity which is only found at pH and temperatures which are not extremes, nor does it teach how to detect false positive under those conditions. In view of the fact that the claims encompass any host cell and any the enzymatic activity being detected, one cannot reasonably conclude that the specification is enabling for the full scope of the claimed invention.

Claim Rejections - 35 USC § 103

10. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

11. As indicated in the Advisory Action mailed on 10/16/23003, claims 1-5 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Yen et al. (US Patent No. 5171684, 1992) in view of More et al. (Appl. Environ. Microbiol. 60(5):1572-1580, 1994). This rejection has been described at length in a previous Office Action mailed on 12/27/2002.

12. Applicants argue that the claim invention distinguishes from the combined references in that claim 1 requires at least "screening in the liquid phase a library of expression clones randomly produced from DNA of two or more uncultivated organisms". In regard to claim 3, Applicants argue that claim 3 requires: (i) recovering DNA selectively from a DNA population derived from two or more uncultivated organisms by contacting the recovered DNA in a liquid phase assay under hybridizing conditions with at least one hybridizing probe containing a full-length coding region sequence or a partial coding region sequence for an enzyme having the specified enzymatic characteristic, (ii) transforming a host cell with the recovered DNA to produce a library of clones; and (iii) screening for a specified enzymatic characteristic in an expression product prepared by expressing the library of clones to obtain expression products, which are screened to identify the specified enzymatic characteristic. Applicants argue that Yen fails to suggest the invention of claims 1 and 3 because in Yen's method, the isolated DNA was

obtained from a single cultured organism and the DNA was pretreated so as to bias the DNA toward a particular known enzyme with a restriction endonuclease whose active site was known to exist in some or all of the genes encoding the predetermined target enzyme. Furthermore, according to Applicants, Yen fails to suggest creating and screening a DNA library that is produced from the DNA of two or more uncultivated organisms or that is randomly produced from DNA of two or more uncultivated microorganisms. In regard to claims 4-5, Applicants submit that Yen does not teach to mutagenize DNA recovered from a mixed population of organisms for formation of a library to be screened for identifying a mutant DNA encoding an enzyme with a specified enzymatic characteristic or having increased pH or temperature stability. Applicants submit that More does not cure the deficiencies of Yen and does not render the claimed invention obvious. According to Applicants, More's disclosure regarding the isolation of DNA from a sediment sample dwells on failure rather than successes. Applicants argue that in view of the teachings of More, one of skill in the art would not be motivated to develop an assay as disclosed by Yen in which the DNA of a mixed population of uncultivated organisms is substituted randomly for the DNA of a single known and cultivated organism to produce a DNA expression library that is screened to identify clones encoding a desired enzymatic activity. Applicants further submit that in view of the inefficiency and lack of reproducibility taught by More, even if one is motivated to combine the disclosures of Yen and More, one of skill in the art would not have a reasonable expectation of success in identifying clones with DNA encoding an enzyme having a desired enzymatic characteristic.

13. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the obviousness rejection. As clearly indicated in previous Office Actions, the Examiner is relying on the teachings of More et al. in regard to the DNA used in the library. The Examiner is not contending that the DNA of Yen was not obtained from a single cultured organism, but rather that Yen teaches a process for identifying clones of a recombinant P.

mendocina KR-1 library where the clones are screened in the liquid phase for toluene monooxygenase activity, i.e. enzymatic activity, using radioactive toluene specificity (column 14, Example 11, Table I) and several other substrates to determine if phenolic compounds were formed, i.e. substrate specificity (column 15-16, Example 12, Table II). More et al. teaches the isolation of DNA from soil microbial populations. Furthermore, More et al. teaches that soil and sediments contain uncultured indigenous microorganisms (page 1572, first column, lines 1-6). Therefore, the limitation "two or more uncultivated organisms" is taught by More et al. In regard to the term "randomly produced", it is noted that the term refers to the clones being produced. As such, this term is implicit since as known in the art, transformation of clones with a DNA library is inherently a random process as (1) not all cells exposed to the DNA will be transformed, and (2) there is no control as to which DNA fragment is going to be present in a particular clone. Therefore, the teachings of Yen and More anticipate the instant claims as written. While it is agreed that Yen does not teach mutagenesis of the DNA prior to transformation of the host cells, as indicated in the Final Action, it would have been obvious to one of skill in the art to mutagenize the DNA prior to its use in preparing the clones. A person of skill in the art is motivated to mutagenize the DNA before preparing the clones to study the effect of mutations in the function of the corresponding protein and to further characterize the structure-function relationship in the protein. One of skill in the art has a reasonable expectation of success at practicing the method of Yen and More with DNA with is mutagenized prior to its use in the preparation of clones since Yen teaches mutagenesis of PmKR1 cells (column 9, Example 4) and DNA mutagenesis techniques are well known and widely used in the art. Therefore, the claimed invention would have been prima facie obvious.

In addition, the Examiner disagrees with Applicant's contention that, in view of More's analysis of the limitations in isolating/purifying DNA isolated from soil, one of skill in the art (1) would not be motivated to develop an assay as disclosed by Yen in which the DNA used is that of

a mixed population of uncultivated microorganisms, and (2) would not have a reasonable expectation of success in identifying clones with DNA encoding an enzyme with a desired characteristic. While it is agreed that More discloses some limitations in regard to the isolation of DNA from soil samples, More does not teach that one of skill in the art cannot isolate DNA from soil samples. In fact, More et al. teaches the improvement of two key steps in DNA isolation from soil samples (Abstract) and conclude that because PCR amplification was indeed possible, the extraction and purification procedures disclosed were successful (page 1579, first column, lines 22-24). Therefore, one of skill in the art would not only be motivated to combine the teachings of More and Yen, but one of skill in the art would have a reasonable expectation of success in identifying clones with DNA encoding an enzyme with the desired characteristic.

Double Patenting

14. Claims 1-5 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims recited in U.S. Patent No. 6280926, 6168919, 5958672, 6,528,249, 6,566,050, as well as in U.S. Application No. 09/421629, 09/467740, 09/875412,

15. As indicated in the Advisory Action mailed on 10/16/2003, in view of the submission of the terminal disclaimer, the double patenting rejections previously applied are hereby withdrawn.

Conclusion

16. No claim is in condition for allowance.

17. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114. It is noted that the claims and arguments submitted under 37 CFR 1.114 were previously presented on 9/22/2003 in response to the Final Office action mailed on 6/18/2004. The amendment filed by Applicants on 9/22/2003 was entered and

addressed in the Advisory Action mailed on 10/16/2003. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

18. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 872-9306. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

19. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (571) 272-0928. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1234.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
July 14, 2004

REBECCA E. PRUTY
PRIMARY EXAMINER
1600